REMARKS

Support for Amendments to the Claims may be found as follows: Original Claim 10; Claim 4 former Step C, and Equation 4 on page 14 of the Specification.

For convenient reference, Pages 2 and following of the Office Action are set forth below in italics with Applicants' responses interlineated:

> *Application/Control Number: 10/057,270 Art Unit: 1631*
> *DETAILED ACTION*
> *Applicant's election without traverse of Claims 4-10,21, 23-24, and 26-32 and the Species of claim 30 in the reply filed on 12/14/2007 is acknowledged.*
> *Applicant's cancellation of claims 1-3, 11-18, 20, and 22 in the response filed 12/14/2007 is acknowledged.*
> *Claims 31 and 33-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventive group, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 12/14/2007.*

Applicants reserve right to file the nonelected Claims 1-3, 11-18, 20, 22, 25 and 31in a separate application or in this application if a linking claim is allowed. Nonelected claims have been cancelled to avoid extra fees.

> *Applicant's arguments, filed 8/32/2007, have been fully considered. The Page 2 following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.*
> *Applicants have amended their claims, filed 8/32/2007, and therefore rejections newly made in the instant office action have been necessitated by amendment.*
> *Claims 4-10,21,23-24,26-30, and 32 are the current claims hereby under examination.*
>
> *Claim Objections*
>
> *Claim 4 is objected to because of the following informalities: Claim 4 comprises inappropriate claim formatting. Each of steps A-E should end in the appropriate punctuation, a semicolon. For example, claim 4, step A inappropriately ends with a period and step B does not end with any punctuation*
> *.Application/Control Number: 10/057,270 Art Unit: 1631*
> *wherein step E ends with an appropriate semicolon. Appropriate correction is required.*

In Claim 4, each step now ends with a semicolon, except for Step G which ends with a period.

Claims 26-39 are objected to for having inappropriate claim numberings. Claim number 25 is missing from the claim numbers. Therefore, claims 26-39 should appropriately be renumbered as claims 25-38.required.

Claims 26-39 are renumbered as 25-38.

Claim Rejections - 35 USC § 112

Response to Arguments:

Applicant's arguments, filed 8/32/2007, with respect to the rejection under 35 USC 112 second paragraph have been fully considered and are persuasive

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because of applicant's amendment. Therefore the rejection has been withdrawn

The following rejections have been necessitated by amendment:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-10,21,23-24,26-30, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4, step A, comprises the term "substantially," which is vague and indefinite and is not defined by the claim. It is unclear as to what constitutes the term "substantially" and/or metes and bounds of said term. Therefore, one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Clarification via clearer claim wording is required.

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The word "substantially" has been cancelled from Claim 4, Step B [formerly Step A] to reduce the objections, but this is not to be construed as narrowing the claim, as those skilled in the Art will appreciate that perfection is not required.

Claim 4, step A, comprises the wording "in a database of sequences of the nucleic acid," which has been deemed as vague and indefinite. It is unclear as to what exactly said wording refers. It appears that the organisms or viruses in a database all comprise a particular nucleic acid along with other sequences in the database for said organisms and viruses. Clarification via clearer claim wording is required.

For clarity, the database is now better defined in a new and separate step as Claim 4, Step A that recites: "A. Obtaining or creating a database of a nucleic acid sequences of a homologous target RNA or DNA, from all organisms or viruses that will be incorporated into the analysis; [per former Step C]. The inclusion of the word "target" allows subsequent

steps to clearly refer to this database of sequences thereby avoiding confusion.

Claim 4, step B, comprises the wording "Identifying the extent to which each particular oligonucleotide or sequence of length N is characteristic of each node," which has been deemed as vague and indefinite. It is unclear as to how each oligonucleotide will be characteristic of each node in the bifurcating node phylogenetic tree.

To clarify the manner in which an oligonucleotide can be characteristic of a node , the phrase "by examining the occurrence frequency of each subsequence in the target nucleic acid of the organisms and viruses encompassed by or not encompassed by each node in the tree;" has been added at the end of Claim 4, Step C (formerly Step B). In order to clarify the text further the word "node" has been deleted from the phrase "bifurcating node phylogenetic tree" as this is more consistent with usual scientific nomenclature. The addition of the qualifier "the presence of" further emphasizes that presence/absence at each node is what is being considered.

As an explanation in answer to: "*It is unclear as to how each oligonucleotide will be characteristic of each node in the bifurcating node phylogenetic tree.*" per the Bioinformatics Genius Blog: "The objective of Phylogenetic [illegible] is the discovery of the branching relationship in the tree and the branch lengths [illegible] analysis of nucleic acid and protein is presently and will continue to be an [illegible] of sequence analysis. In addition to analyzing changes that have occurred [illegible] of different organisms the evolution of family of sequences may be studied [illegible] Identifying sequences that are closely related can be identified by their [illegible] neighboring branches on a tree. When a gene family is found in an organism [illegible] organism phylogenetic relationship among the genes can help to predict [illegible] have an equivalent function. Phylogenetic analysis may also be used to follow [illegible] changes occurring in a rapidly changing species such as Virus. Analysis of [illegible] viral gene with in a population can reveal, for example, whether or not a [illegible] immune selection an important source of information in applications like Epidemiology [illegible] tree of sequences, it should be possible to find the genealogical ties between [illegible] organisms. Experience learns that, closely related organisms have [illegible] more distantly related organisms have more dissimilar sequences. One [illegible] the evolutionary relationship between species. Another objective is to [illegible] the divergence between two organisms since they last shared a [illegible]

Claim 4. step B. comprises the wording "each particular oligonucleotide or sequence of length N," which has been deemed as vague and indefinite. It is unclear as to which sequences or oligonucleotides are being referenced. For instance, it is unclear as to the exact differences between the sequences in the database and the nucleic acid and therefore it remains vague and indefinite as to which sequence is being referenced in the instant vague and indefinite wording. Clarification via clearer claim wording is required.

The term "oligonucleotide sequence of length N" is replaced by "RNA or DNA subsequence of length N" This clarifies Claim 4 Step C [formerly Step B] by distinguishing the complete nucleic acid sequences of the target nucleic acid in the database of current Claim 4, Step A from the small subsequences of length N that will occur in some sequences but typically not all. The distinction is emphasized by including the phrase "target nucleic acid" which provides clear reference to the sequences in the database of Claim 4 Step A and thereby clarifies the distinction from the subsequences of length N. .

Claim 4. steps B and C are deemed as vague and indefinite. It is unclear as to how identifying how each particular oligonucleotide is characteristic of each node plays a role in creating or deriving a signature database of signature sequences. If each of steps A-F are independent of each other, then it is equally vague and indefinite as to how the signature database is created or how "signature probes" are derived from said signature database. Clarification via clearer claim wording is required.
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Claim 4, Preamble now recites steps "in combination". In order to further clarify Step B (the previous Step C) and Step E (previous Step C) a new Step D has been added that describes the database that is subsequently referred to in Step E. For clarity and consistency of wording, Step C (previously Step B) now reads: "C. ~~B.~~ Identifying the extent to which the presence each particular RNA or DNA subsequence of length N is characteristic of each node in the bifurcating phylogenetic tree of genetic relationship...;"

Claim 4, step C, comprises the wording "Deriving a plurality of nucleic acid signature probes from a signature database of signature sequences," which has been deemed as vague and indefinite. It is unclear as to what exactly a "signature database" comprises. Furthermore, it is unclear as to what the wording "signature probes" or "signature sequences" mean. For instance, it appears that "signature sequences" may be consensus sequences or conserved sequences across different organisms. In addition, because it is unclear as to what the wording "signature sequences" or "signature probes" refers, it further unclear as to how these probes are used to identify twice the number organisms as number of probes used. Clarification via clearer claim wording is required.

The addition of new Claim 4 Step D clarifies the phrase "signature database" and what it comprises. The additional wording in Claim 4 Step C (previously Step B) "by examining the occurrence frequency of each subsequence in the target nucleic acids of the organisms and viruses encompassed by or not encompassed by each node in the tree;" clarifies that the signature value of a particular N-mer at a particular node is based on frequency of occurrence among organisms encompassed by the node and those excluded from the node. This makes it clear that signature sequences as defined herein need not be consensus sequences or conserved sequences. In view of the improvements in the wording of Step C (previously Step B) and the addition of Step D, Step E (previously Step C) now clearly defines "signature probes" as "sequences that will be complementary to a portion of the target nucleic acid sequence of the organism or virus if the signature sequence is present" The plurality of probes selected will be chosen to encompass numerous nodes in the tree, including large ones. For example, if one of the nodes encompassed by the set of probes were the Gram positive bacteria, then that genetic affinity would be detected for any of thousands of bacteria without increasing the number of probes.

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Claim 4, step C, comprises the wording "the nucleic acid sequence," which

has been deemed as vague and indefinite. It is unclear as to which nucleic acid sequence of the organism or virus is being referenced. Clarification via clearer claim wording is required.

Claim 4. Step A now addresses this issue by pointing out that any homologous (e.g. functionally equivalent) RNA or DNA can be used. The RNA or DNA chosen is referred to as the target sequence. Subsequent parts of the claim such as Step E (formerly Step C) now incorporate the phrase "target nucleic acid" in order to clarify what is meant.

Claim 4. step C, comprises the wording "the number of organisms or viruses whose genetic affinity might be determined is at least twice the number of probes used." which has been deemed as vague and indefinite. It is unclear as to what exactly the word "might" refers. It is unclear as to whether the signature probes are actually capable of identifying twice the number of different organisms or viruses as the number of probes used or if the wording might be referring to twice the number of the same organisms. It is unclear as to
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what determines the potential of the probes for identifying the genetic affinity of twice the number of organisms or viruses in a sample than the number of probes used in cases wherein twice the number of organisms or viruses are not identified, which is what the word "might" infers. Clarification via clearer claim wording is required.

"Might" has been cancelled from Claim 4E [formerly Step C] and replaced with –can-- to better express the ability of the invention as claimed.

Claim 4. step F, comprises the vague and indefinite wording "which nodes in the bifurcating node phylogenetic tree of genetic relationship produced detectable signal." It is unclear as to how the nodes produce detectable signals. It remains further unclear as to how the detectable signals result in a determination of identifying the closest genetic relatives of the organism or virus in the test sample. Clarification via clearer claim wording is required.

Claim 4 Step H (Previously Step F) now reads "Using the database of characteristic signature sequences to determine the nodes in the bifurcating phylogenetic tree of genetic relationship that are represented by the signature probes that produced detectable signal in order to identify the closest genetic relatives of the organism or virus in the test sample." This new text wording makes it clear that

the signals come from the probes, not from the nodes they represent. The new wording also clarifies "how the detectable signals result in a determination of identifying the closest genetic relatives..." by explicitly making a link to the database of signature properties of each N-mer.

As to "*how the nodes produce detectable signals*", Page 8 of the Specification explains that: A hybridization signal can comprise fluorescence, chemiluminescence, or isotopic labeling, etc.; or sequences in a sample can be detected by direct means, e.g. mass spectrometry.
Page 32 further explains: "Hybridization can also lead to production of signals by self-quenching probes such as molecular beacons, or by ribozyme activation, FRET pairs, or changes in plasmon resonance or similar interfacial optical phenomena, in mechanical resonant frequency, in redox activity or electrical conductivity, in electrophoretic or chromatographic mobility, in affinity for chelated metals, minerals, or antibodies or proteins, or in particle or molecular mobility."

As to: "*...how the detectable signals result in a determination of identifying the closest genetic relatives of the organism or virus in the test sample*": page 3 of the Specification reads: "The method of this invention is currently most readily utilized with 16S rRNA sequence data but can be adapted to other data sets such as rRNA spacers, RNAse P RNA, genomic DNA or RNA of viruses, etc. One begins by defining microbial groups within a phylogenetic tree that includes the organism range of interest, e.g. all bacteria for example. Then a set of characteristic oligonucleotides, each of which identifies a group in the phylogenetic tree is determined according to a newly developed algorithm of the invention. This set of signature oligonucleotides is utilized in a hybridization experiment, e.g. a DNA microarray, the results of which are then used to quickly identify the phylogenetic neighborhood of a problematic bacterium, or other microorganism.
And page 16 of the Specification explains: "When the program tree parser parses the tree file and builds the internal tree structure, only the abbreviated and full names of the organism are kept for each leaf node and all other information is discarded. The abbreviated name is later compared with every name in the set of matched organisms of every oligonucleotide to determine if this leaf node is matched by a particular oligonucleotide."

> *Claim 10. step A and step B. comprises the wording "substantially homologous RNA or DNA" and "substantially every oligoribonucleotide." which*
> *has been deemed as vague and indefinite. It is unclear as to what constitutes the term "substantially" and/or metes and bounds of said term. Therefore, one of ordinary skill in the art would not be reasonably appraised of the scope of the*
> *invention. Clarification via clearer claim wording is required.*

The word "substantially" has been cancelled from Claim 10, Steps A and B. However, this does not narrow the claim as "substantially" is cancelled merely to remove a formal objection and expedite prosecution, not to change the meaning nor to avoid some prior art.

> *Claims 23 and 30, the equation variables NGM2 and "N GM" have been deemed as vague and indefinite. It is unclear as to whether NGM2 is defined as the same as NGM or is a separate variable without properly being defined Furthermore, it is unclear as to whether "N GM" are two separate variables without proper definitions or the same variable as "NGM." Clarification via clearer claim wording is required.*

In Claim 23 and 29 [formerly 30] the spacing error has been corrected and the proper letters shown as subscripts and proper numerals shown as superscripts to conform to Equation 4 on page 14 of the specification.

> *Page 6*
> *Application/Control Number: 10/057,270 Art Unit: 1631*
> *Claim 26 is being rejected because it comprises a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim), which is considered indefinite, since the*
> *resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the*
> *Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App.*
> *1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 26 recites the broad*
> *recitation wherein 15 sequences are used to determine the genetic affinity of at*
> *least 18 organisms, and the claim also recites the number of organisms or*
> *Page 7*
> *viruses whose genetic affinity might be determined is at least twice the number of probes, which is the narrower statement of the range/limitation.*

The cited limitations in Claim 26 are not a broad and a narrower recitation of the *same* range. Instead, they are recitations of two *different* ranges: (a) the number of sequences used and (b) the ratio of moieties whose genetic

affinity is determined per probe. Thus, *Ex parte Wu* does not forbid reciting two *different* ranges (See MPEP 2173.05(h) Alternative Limitations.) There is no "such as" in the Claim.

> *Claim 27 has been deemed as vague and indefinite. It is unclear as to how the failure to detect a particular sequence results in increased confidence with which the genetic affinity of an organism or virus is determined Clarification via clearer claim wording is required.*

Page 9 of Applicants' specification explains that: "Ultimately, even if nothing matches, the invention nonetheless gives useful information. For example, it might be learned that the unknown organism belongs to the group of enteric bacteria but is not any of the known species."

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> *Claim 28 is being rejected because it comprises a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim), which is considered indefinite, since the*
> *resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the*
> *Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App.*
> *1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 28 recites the broad*
> *recitation wherein more than one oligonucleotide or sequence is detected, and*
> *the claim also recites the number of organisms or viruses whose genetic affinity*
> *Page 8*
> *might be determined is at least twice the number of probes, which is the narrower statement of the range/limitation.*

The cited limitations in Claim 28 are not a broad and a narrower recitation of the *same* range. Instead, they are recitations of two *different* ranges: (a) the number of sequences used and (b) the ratio of moieties whose genetic affinity is determined per probe. Thus, *Ex parte Wu* does not forbid reciting

two *different* ranges (See MPEP 2173.05(h) Alternative Limitations.) There is no "such as" in the Claim.

> *Claims 5-9, 21, 24, 29, and 32 are rejected as being dependent from a rejected claim.*

The formal objections to Claim 4, on which all these Claims depend directly or indirectly, having been addressed above, it is urged that these dependent Claims are now in condition for allowance.

> *Claim Rejections - 35 USC § 103*
> *Response to Arguments:*
> *Page 9*
> *Application/Control Number: 10/057,270 Art Unit: 1631*
> *Applicant's arguments, filed 8/23/2007, with respect to the rejection of claims under 35 USC 103 have been fully considered and are persuasive because of applicant's amendments and arguments. Therefore the rejection has been withdrawn.*

The Examiner is thanked for withdrawing the prior rejections under 35 U.S.C. 103.

> *The following rejection has been necessitated by amendment:*
> *Claim Rejections - 35 USC § 102*
> *The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this*
> *Office action:*
> *(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351 (a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21 (2) of such treaty in the English language.*
> *Claims 4-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Ebersole et al. (US P/N 6,797,817).*
> *The claims are directed to a method for determining the genetic affinity of organisms or viruses in a test sample containing a nucleic acid comprising the steps of:*
> *A) Obtaining or developing a bifurcating node phylogenetic tree that substantially reflects the genetic relationship between the organisms or viruses*
> *included in a database of sequences of the nucleic acid.*
> *B) Identifying the extent to which each particular oligonucleotide or sequence of length N is characteristic of each node in the bifurcating node phylogenetic tree of genetic relationship.*
> *Page 9 Application/Control Number: 10/057,270 Art Unit: 1631*

C) Deriving a plurality of nucleic acid signature probes from a signature-database of signature sequences that are complementary to a portion of the nucleic acid sequence of the organism or virus such that the number of
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organisms or viruses whose genetic affinity might be determined is at least twice the number of probes used.
D) Hybridizing the signature probes to the nucleic acid obtained from the test sample under conditions where a detectable signal will be produced by signature probes that hybridize to the nucleic acid of the organism or virus.
E) Identifying signature probes which produce detectable signal.
F) Determining which nodes in the bifurcating node phylogenetic tree of genetic relationship produced detectable signal to identify the closest genetic relatives of the organism or virus in the test sample.
Ebersole et al. teaches at Col. 9, lines 35-45 that a phylogenetic Tree of Life was obtained and used for extracting sequences that represented the major microorganism domains, Bacteria and Archeae, which could be used as signature sequences for obtaining signature probes for testing for the presence
of dechlorinating bacteria, which reads on method steps A-C. Furthermore, Ebersole et al. teaches at col. 4, lines 55-67 and col. 5, lines 1-4, that sequence
profiles, from which signature probes are derived, may be used to identify and subtype bacteria with similar metabolic pathways. Therefore, a signature probe
may be used to identify a dechlorinated bacteria and/or bacteria with similar metabolic pathways, such as subspecies of decholorinates, which further reads
on step C) Deriving a plurality of nucleic acid signature probes from a signature-
database of signature sequences that are complementary to a portion of the nucleic acid sequence of the organism or virus such that the number of
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organisms or viruses whose genetic affinity might be determined is at least twice the number of probes used. Ebersole et al. further teaches at col. 4, lines 55-67 and col. 5, lines 1-4 that the use of particular sequences may be used to identify decholorinators as well as for genetic sub-typing of species, which further reads on method step B) Identifying the extent to which each particular oligonucleotide or sequence of length N is characteristic of each node in the bifurcating node phylogenetic tree of genetic relationship.
Ebersole et al. further teaches at col. 2, lines 51-65, the use of signature probes in hybridizing to identifying sequences such that a signal is detectable, which reads on step D) Hybridizing the signature probes to the nucleic acid obtained from the test sample under conditions where a detectable signal will be produced by signature probes that hybridize to the nucleic acid of the organism or virus. Ebersole et al. at col. 5,lines 34-39, col. 6, lines 31-34, col. 6, lines 58-67, and col. 7, lines 1-9 teaches using signature sequences for generating probes and defines the use of probes and hybridization as such that is consistent in the art, which produce detectable signals, which reads on step E) Identifying signature probes which produce detectable signal.
Ebersole et al. teaches at col. 8, lines 38-40 that the sequences are useful for the identification of new dechlorinating bacteria, as well as for sub-typing strains of Dehalococcoides ethenogenes. Furthermore, Ebersole et al. teaches at col. 9, lines 19-40 that sequences used for obtaining probes and closest or nearest organisms to these sequences were determined.
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> *which all read on step E) Determining which nodes in the bifurcating node phylogenetic tree of genetic relationship produced detectable signal to identify the closest genetic relatives of the organism or virus in the test sample Ebersole et al. teaches claim 5 at col. 2, lines 50-59 wherein rDNA are used for obtaining probes, which reads the use of DNA for comprising signature*
> *probes.*
> *Page 12*
> *Ebersole et al. teaches claim 6 at col. 6, lines 58-67 wherein hybridization is taught with that which is consistent in the art wherein a hybridization step is done in solution, which reads on claim 6.*
> *Ebersole et al. teaches claim 7 at col. 13, lines 25-30 wherein it is taught that probes which generate a detectable signal are used, which inherently reads on a probe wherein the detection step utilizes radioactive labels, chemiluminescence, and/or fluorescence.*

The rejection under 35 U.S.C. 102 of Claims 4-7 on Ebersole et al. (Ebersole) must be respectfully traversed. To support a 35 U.S.C. 102 rejection, *every* element of the rejected claim must be taught by the reference.

Ebersole, like the Barns reference distinguished in the previous response, does not teach any method for analyzing *what* is in the sample, only whether or not a particular organism or type of organism is present, e.g. dechlorinating bacteria. For example, Ebersole's only claim reads:

> *1. An isolated 16S rDNA sequence indicative of a dechorination bacterial strain selected from the group consisting of:*
> *(a) Seq ID No:8, and (b) an isolated nucleic acid molecule that is* ***completely complementary*** *to (a) wherein said sequence is indicative of a dechlorinating bacterial strain.*

In contrast, the powerful present invention determines the genetic affinity of *any* organism or virus in the sample. Indeed, it is not even necessary that the organism had been encountered previously by the scientific community. This is possible because the Applicant's method focuses on genetic affinity (closest relatives among previously studied organisms) rather than specific identity. Thus,

Ebersole does not teach us "to determine the nodes in the bifurcating phylogenetic tree of genetic relationship that are represented by the signature probes that produced detectable signal..." as recited in Step H [formerly F] of Applicants' Claim 4. In fact, by seeking to determine the presence of a specific group of organisms whose identity is known ahead of time, Ebersole actually *teaches away* from the present invention.

Moreover, Ebersole relies on the presence of a single sequence AND his sequence must be completely complementary to the target organism's 16S rDNA. This also teaches away from the present invention by suggesting that one must have specific sequences for every target of interest and therefore that sequences that are not complete complements are not useful. In contrast, page 9 lines 11-12 of the present Application states: "The invention can identify the genetic grouping an unknown organism belongs to even if no perfect match is found."

The present Application teaches that sequences with signature quality scores well less than perfect can in fact be very useful. In order to take advantage of the information carried by such signature sequences, the present Application (see p.7 lines 9-11) teaches the use of a "plurality" of such signature probes that target many separate groupings, not just one. Here again, Ebersole *teaches away* by teaching a procedure that by its very nature can only produce probes(s) for specific groupings.

Further, the present Application teaches that nucleic acids other than 16S rRNA or 16S rDNA can be used. Thus, for example, Applicants' method can be used with the genomic RNA of flaviviruses, which do not have a 16S rRNA.

Regarding Applicants' Claim 4, method steps A-C: Ebersole et al. teaches at Col. 9, lines 35-45 that a phylogenetic Tree of Life be obtained and used for extracting sequences that represent the major microorganism domains, Bacteria and Archeae, which can used as signature sequences for obtaining signature probes for testing for the presence of dechlorinating bacteria.

Ebersole utilizes the tree of life for a different purpose than in the present invention. Ebersole uses the tree to identify organisms whose rRNA or rDNA sequences will be useful in identifying **signature sequence regions** that in turn might contain signature sequences (See Ebersole Col. 17 lines 17-28 and col. 18 lines 1-15). These signature *regions* are areas (regions) within which Ebersole searches for signature sequences. Ebersole's tree is only used for selecting organisms whose sequences are then used in a sequence alignment from which signature *regions* are defined. The actual relationships are not important to Ebersole.

In the present invention, the tree is used to define the signature properties of every oligonucleotide of interest. This can be done ahead of time as would be the case of the design of a hybridization array, or after the fact, as might be done in a case where the

signature sequences are physically produced and then identified, e.g. by digestion of an RNA with a ribonuclease. Individual sequences are never extracted from the database and no alignment is done. Applicants' tree is not used to select organisms. Instead Applicants' tree relates the occurrence of each candidate signature sequence to the various groupings in the tree. The distribution of each member in a set of candidate signature sequences, e.g. all 15mers, relative to each node in the tree is determined. Thus page 6 lines 14-16 of the Application states :

> "D. Test all possible sequences of this length N against the entries in the nucleic acid sequence database that is being used in conjunction with the tree. A signature quality function such as Q_s is calculated for every possible sequence of length N at each node in the tree."

Ebersole does not use his tree in this manner and in fact never calculates the occurrence frequency and distribution of oligoribonucleotide or oligodeoxyribonucleotide sequences of length N in his sequence.

It is important to point out here that Ebersole uses the term "signature sequence" in a meaning that is different from the present Application. In particular, Ebersole refers to sequences that are uniquely found in targets of interest and not found elsewhere, e.g. sequences that have very high "inclusivity" and "exclusivity" in the nomenclature of the Barnes reference. Thus, at his column 2 lines 41-47 Ebersole writes:

> *"The problem to be overcome is to identify a UNIQUE 16S rDNA sequence in bacteria capable of dechlorination of persistent chlorinated compounds for the identification and*

ultimate enhancement of that bacteria to remediated a contaminated site. Applicants have solved the stated problem by providing a set of nucleic acid sequences that are UNIQUE *to various strains of Dehalococcoides ethenogenes."*

C) Deriving a plurality of nucleic acid signature probes from a signature-
database of signature sequences that are complementary to a portion of the
nucleic acid sequence of the organism or virus such that the number of
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organisms or viruses whose genetic affinity might be determined is at least twice the number of probes used.

STEP C

Regarding Applicants' Step C, Ebersole teaches at his col. 4, lines 55-67 and col. 5, lines 1-4, that sequence profiles, from which signature probes are derived, can be used to identify and subtype bacteria with similar metabolic pathways. Therefore, a signature probe can be used to identify a dechlorinated bacteria and/or bacteria with similar metabolic pathways, such as subspecies of decholorinates.

In contrast, Step A [formerly C] of Applicants' Claim 4 recites a database which comprises the signature properties of large numbers of N-mers. Ebersole never creates such a database and instead teaches away from it by emphasizing the need to find and use small numbers of sequences that are as unique as possible to the target organisms. On p. 7 line 1 of the Application, it is pointed out that the current invention works to "retain as signature sequences those test sequences having values of Qs above some criterion". That criterion need not be 1 or even close to 1. For example, a signature sequence may occur in 90% of the organisms or viruses in one grouping. 70% of the organisms or viruses in another grouping and 45% in a third

grouping. It would thus have a different Qs score for each grouping and each of these scores would be well below the perfect score of 1.0. (see p. 7, lines 1-4, and p. 22 lines 1-2 of the Applicant's application). That one can use such N-mers (subsequences) according to the present invention is extremely unexpected and non-obvious. The present invention teaches that such sequences with signature quality scores well less than perfect can in fact be very useful. For instance, in the example given above they contribute to the recognition of three distinct organism or virus groupings rather than just one. In order to take advantage of the information carried by such signature sequences, the present invention (p.7 lines 9-11) teaches the use of a "plurality" of such signature probes that target many separate groupings, not just one. Thus, an array of probes constructed from sequences in the signature sequence database can be constructed that can determine the genetic affinity of large numbers of diverse organisms regardless of any similarity of metabolic function. Ebersole teaches away from this conclusion by emphasizing that his bacteria must share similar metabolic pathways. In fact, photosynthetic bacteria of various types do share similar photosynthetic pathways, but in terms of genetic affinity are not sufficiently related to be identified by a single signature probe of the Ebersole type. So not only does Ebersole et al., teach away from the current invention, his suggestion is not generally valid.

Step D

Regarding Applicants' Step D, Ebersole teaches at his col. 2, lines 51-65, the use of signature probes in hybridizing to identifying sequences such that a signal is detectable.

The nine probes described by Ebersole at his col. 2 lines 51-59 are all essentially unique to particular dechlorinating bacteria. These are all N-mers with very high or perfect Qs scores and hence can not determine genetic affinity of an unknown organism. Ebersoles' probes are instead targeted at identifying one specific group of bacteria. The probes listed by Ebersole do not include most of the preferred signature probes that are taught in Applicants' invention, whose presence is essential to determining genetic affinity without prior knowledge of what organism is present in a test sample.

Moreover, the invention of Claim 4 is unique in its combination of steps A, B, C, D, E, and F.

STEP E

Regarding Applicants' Step E, Ebersole at col. 5,lines 34-39, col. 6, lines 31-34, col. 6, lines 58-67, and col. 7, lines 1-9, teaches the use of signature sequences for generating probes and defines the use of probes and hybridization as such that is consistent in the art, which produce detectable signals.

The probes used by Ebersole et al. are not signature probes in the sense of the current invention. Ebersole *et al.* define signature sequences on column 5 lines 34-37 as:

> "The term "signature sequence" or signature sequence region or signature groups will refer to those short sequences in the 16S gene or RNA molecule which are UNIQUE to a certain group or groups of organisms" [Emphasis added].

Ebersole's requirement for uniqueness (as emphasized in our earlier response to Barnes), distinguishes signature sequences as defined by

Ebersole from signature sequences as defined by the present Application. Signature sequences as used in the present invention are informative about the genetic affinity of the organism or virus carrying the nucleic acid. They are absolutely not required to be unique to any target group, whether that target group be a species, a genus or some other taxonomic unit. Thus, p. 7 line 1 of the Application indicates that the invention works to "retain as signature sequences those test sequences having values of Qs above some criterion". That criterion need not be 1 or even close to 1. For example, a signature sequence may occur in 90% of the organisms or viruses in one grouping, 70% of the organisms or viruses in another grouping and 45% in a third grouping. It would thus have a different Qs score for each grouping and each of these scores would be well below the perfect score of 1.0. (see p. 7, lines 1-4, and p. 22 lines 1-2 of the Applicant's application). That one can use such N-mers (subsequences) according to the present invention is extremely unexpected and non-obvious and pointed out by the fact that both Barnes and Ebersole et al. emphasize that sequence must have high "inclusivity" or be "unique." In addition Step E has no requirement that the nucleic acid be 16S rRNA or 16S rDNA. Finally, the invention of claim 4 is unique in its *combination* with steps A, B, C, D, E, and F.

STEP F

The examiner does not point to any part of Ebersole that may read on step F. Therefore the invention of claim 4 is unique from Ebersole *et al* in the addition of Step F.

Ebersole et al. teaches claim 5 at col. 2, lines 50-59 wherein rDNA are

used for obtaining probes, which reads the use of DNA for comprising signature
probes.

Claims 5-7: Ebersole does not teach applying the specific techniques recited in Claims 5-7 to signature sequences. These are dependent claims and Ebersole is not meeting the recitations of Claim 4 as per above discussion.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire
THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory
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action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.
Conclusion
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Marjorie Moran can be reached via telephone (571)-2720720.
Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pairdirect.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
/J Sims/
/Michael Borin, PhD
Primary Examiner, Art Unit 1631
Application/Control Number: 10/057,270 Art Unit: 1631

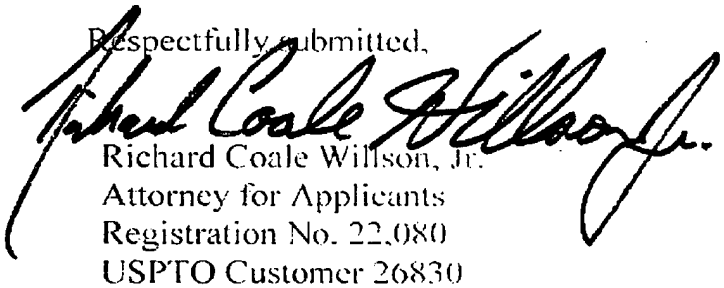
Applicants' note that this is a Final Rejection and have replied within two months. Amendments are made merely to improve the clarity of the claims and no estoppel is involved.

Any other necessary (small entity) charges can be charged to USPTO Deposit Account 20-336 of Technology Licensing Co. LLC.

Correspondence may be addressed to Customer No. 26830.

The Examiner is especially invited to suggest allowable subject matter and to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,



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